REMARKS

1. Overview of Claim Amendments

Applicants request a telephonic interview with Examiner Mondesi and his SPE to discuss the instant amendments. We would like to hold the interview in April so that if further amendments seem appropriate, they can be filed during the period of suspension requested in the instant RCE.

1.1. Original claim 1 was directed to a fusion in which (i) the first polypeptide sequence comprised at least thirty consecutive amino acids of any lectin complement pathway-activating protein, or a sequence at least 70% identical thereto, and (ii) the second polypeptide sequence comprised at least thirty consecutive amino acids of any collectin, or a sequence at least 70% identical thereto.

Claim 1 has been cancelled, and we have rewritten claims 58, 27 and 67 in independent form. The rewritten claims are broader than the former dependent claims, but substantially narrower than the former claim 1.

All three independent claims now require the lectin complement pathway activating protein of former claim 1, paragraph (i), to be human L-ficolin, and the collectin of paragraph (ii) to be human MBL, consistent with the elected fusion protein[1]. They thus read on fusions of a fragment of human L-ficolin with a fragment of human MBL, per the elected species.

All three independent claims require the fusion protein to retain the activities attributed by claim 1 to the first and second polypeptide sequences.

All three independent claims provide that the fusion protein

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[1] It is disclosed that the first polypeptide sequence is "derived from a lectin-complement pathway activating protein or from a functional homologue thereof" and the second polypeptide sequence is "derived from a calectin or from a functional homologue thereof". P9, L27-34. More preferably, the "first polypeptide sequence is derived from L-ficolin or from a variant or homologue of L-ficolin" (P11, L5-6) and the collectin of the second sequence is MBL (P20, L3-4).

does not comprise human l-ficolin per se and does not comprise human MBL per se, i.e., they require fusion of a fragment (or certain mutants thereof) of L-ficolin to a fragment (or certain mutants thereof) of MBL.

All three independent claims limit mutation such that the mutant sequence is the result of amino acid substitution and at least 95% identical to the reference fragment sequence[2].

The three differ in terms of how the fragments are defined. The table below compares how claims 58, 27 and 67 handle fragments, and also compares the claim language to the fused fragments of the elected species and the exemplified species.

Table I		
Claim	**human L-ficolin fragment**	**human MBL fragment**
58	comprises at least 40 consecutive amino acids	comprises at least 50 consecutive amino acids
27	comprises collagen-like domain[3]	comprises CRD domain
67	comprises at least amino acids 1-44	comprises at least amino acids 100-200

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[2] P85, L5-8 discloses "in the present context the terms homologue or variant or functional homologues are used as synonymes, wherein a homologue of a protein exhibits one or more substituions [sic], deletions, and/or additions of one or more amino acid residues. Fragments are a subgroup of homologues being truncations of the protein".

Thus, it provides basis for limiting the fusions to fusions of (1) fragments, and (2) substitution mutants of such fragments. Cp. P87, L27 ("may comprise addition or deletion", implicitly discloses the alternative, does not comprise it).

Claims asserting at least 95% identity have been presented previously, and the basis is at P18, L37 for the first polypeptide sequence, and at P81, L50 for the second polypetpide sequence.

[3] Basis for this formulation of claim 27, i.e., without reference to the cysteine-rich region, exists at page 11, lines 5-7.

Elected species (SID 127)	*amino acids 1-77*	*amino acids 80-228*
made, test data in spec (see tables 4 and 5)		
r4(SID121)[4]	1-57	56-228
r5(SID122)	1-44	44-228
made but no test data in spec., test data in poster (Ex. D)		
r1(SID118)	1-103	106-228
made, no test data in spec		
r2(SID119)	1-181	106-228
r3(SID120)	1-67	81-228
r6(SID123)	26-67	80-228 (and 1-21)
r7(SID124)	1-67	80-228

The Examiner's attention is also directed to the sequence alignment presented in Fig. 9.

1.1.1. The Examiner will note that claim 58 requires 40 consecutive amino acids of human L-ficolin. Basis for this amendment (broader than prior 58 but narrower than prior 1) appears at P18, L34.

As the Examiner can see from Table 1 above, applicants have made a functional mutant r5 (SID 122) which takes only residues 1-44 from human L-ficolin. It therefore did not appear appropriate to require applicants to include, in their claimed fusion protein, 50 consecutive amino acids of human L-ficolin, per the prior language of claim 58. Such would be an invitation to competitors to exploit applicant's reduced-to-practice r5 fusion without any consideration to applicant. If L-ficolin fragments other than the tested 1-44, 1-57 and 1-103 fragments are not functional, they are expressly excluded by the functional limitation of claim 58 paragraph (i).

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[4] SEQ ID NOs:118-124 each consist of a 25 a.a. signal sequence, together with the indicated sequences of mature L-ficolin (SID 125) and mature MBL (SID 126).

The original "at least fifty" language of claim 58 is now presented in claims 77 and 78.

1.1.2. Claim 67, for the same reasons, recites that the reference fragment of L-ficolin comprises at least amino acids 1-44 thereof. See also claim 68. The original language of 67, "at least amino acids 1-54", have been moved to claims 79 and 80.

Claims 61 (dependent on 58), 63 (dependent on 67), 74 (dependent on 27), and 75 (dependent on 71) further limit the nature of the mutations (if any) to conservative substitutions, which are defined by page 85, lines 22 to page 8, line 8.

We have also presented dependent claims which require 100% rather than 95% identity. These include:

70 (dependent on 27)

76 (dependent on 58)

68 (dependent on 67).

1.2. To appreciate the basis for claims 87-89, the Examiner should consider Table II below, which shows the source of various elements of the exemplified r1, r4a dn r5 mutants and their positions in the source proteins L-ficolin and MBL.

Table II

	Cys-rich region	collagen-like domain	neck	CRD
SID127 (1-77 ficolin + 80-228 MBL)	L-ficolin	L-ficolin (complete)	MBL	MBL
SID 118 (r1) (1-103 ficolin + 106-228 MBL)	L-ficolin	L-ficolin (complete)	hybrid (mostly L-ficolin)	MBL
SID 121 (r4) (1-57 ficolin + 56-228 MBL)	L-ficolin	hybrid	MBL	MBL
SID 122 (r5) (1-44 ficolin + 44-228 MBL)	L-ficolin	hybrid	MBL	MBL
L-ficolin	1-25	26-67	n/a	n/a

MBL	1-21	22-79 or 22-80	81-110 or 80-113	111-228 or 114-225

Appendix 3 (Table III) compares all of the fusion protein claims.

2. Allowable Subject Matter

We thank the examiner for indicating that claim 30 defines allowable subject matter. Claim 30, directed to the fusion protein of SEQ ID NO:127, fig. 3, was merely objected to as dependent on a rejected base claim. This SID 127 is effectively residues 1-77 of human L-ficolin (SID 125) joined to residues 88-228 of human MBL (SID 126). It is also the species we elected in response to the species restriction.

Claim 30 is now dependent on amended claim 58, which we consider to be allowable.

3. Election/Restriction

3.1. We added new claims 66-69 in the last amendment. Of these, claims 67 and 68 were withdrawn from consideration as drawn to an unelected invention.

Claim 68 requires a fusion protein comprising (i) at least amino acids 1-54 of human L-ficolin (SID 125) and (ii) at least amino acids 100-200 of human MBL (SID 126).

Claim 67 parallels claim 68 but permits variants with at least 95% identity.

The elected species was SID 127, consisting of residues 1-77 of human L-ficolin (SID 125) and 88-228 of human MBL (SID 126).

The term "at least amino acids 1-54 of human L-ficolin" reads on the elected 1-77, and "at least amino acids 100-200 of human MBL" reads on the elected 88-228.

Since claims 67 and 68 read on the elected species, they shouldn't have been withdrawn. In the interview of February 12,

2007, the Examiner agreed to rejoin these claims[5], as well as claims 5, 6, 7, 18, 29, 57, 59, 60, 61 and 63 (underlined claims are still pending after this amendment).

3.2. Claim 58 was examined. Claim 58, as now amended, is intermediate in scope between its former base claim 57 (previously deemed withdrawn, but which the Examiner agreed to rejoin[6]; it is now cancelled in favor of 58) and claim 58 as previously presented.

Amended claim 58 still reads on the elected species[7]. First, its fusion protein comprises a first sequence which is "at least 95% identical" to a sequence comprising "at least forty consecutive amino acids of human L-ficolin. The elected first piece of the fusion protein species is 100% identical to amino acids 1-77 of human L-ficolin.

Secondly, amended claim 58 recites that the fusion protein comprises a second sequence which is "at least 95% identical" to a sequence comprising "at least fifty consecutive amino acids" of human MBL. The second piece of the elected fusion protein is 100% identical to amino acids 80-228 of human MBL.

3.3. Dependent claims 56 (now on 58), 61 (now on 58), 63 (now on 67), likewise do not exclude the elected species.

3.4. With respect to amended claim 27, to appreciate why it reads upon the elected species, we must examine the domain structure of human L-ficolin and human MBL.

The domain structure of mature MBL was discussed at page 22

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[5] The interview summary record of February 13, at page 2, mistakenly referred to claim "69" when 67 was intended, cp. page 1.

[6] Since claim 58, as previously presented, was deemed to read on the elected species, the broader claim 57 must too.

[7] Amended 58 is similar to withdrawn claim 60, although it recites "forty" rather than "fifty" re human L-ficolin. Applicants note that for the reasons explained in the February 13, 2008 interview summary record, the withdrawal of claim 60 was improper, and the Examiner agreed to rejoin this claim. However, claim 60 is now cancelled in favor of amended 58.

of the October 1, 2007 response:

cysteine-rich region	AAs	1-21
collagen-like domain		22-80
neck region		81-110
CRD		111-228

Slightly different domain boundaries may be deduced from the discussion of Swiss Prot entry MBL2_HUMAN (P1126) (Exhibit A) after subtracting out the 20 a.a. signal:

cysteine-rich region	1-21
collagen-like domain	22-79
neck region	80-113
CRD	114-225

Swiss Prot entry FCN2_HUMAN (Q15485) (Exhibit B) yields the following approximate domain structure for human L-ficolin:

collagen-like domain	26-67
fibrinogen-like domain	106-252

(and thus the cysteine-rich region, which precedes the collagen-like domain, see Exhibit C, is AAs 1-25).

It is clear from the foregoing that a sequence comprising the collagen-like domain of human L-ficolin reads upon the elected species' 1-77 of human L-ficolin, and a sequence comprising the CRD domain of human MBL reads upon the elected species' 80-228 of human MBL.

3.5. The same analysis also justifies joinder of claims 21, 22, 24 and new claims 70-72.

3.6. In the Interview of February 12, 2008, Examiner Mondesi agreed to rejoin at least claims 68, "69" [sic, "67"], 5, 6, 7, 18, 29, 57, 59, 60, 61 and 63. Note the relationship of claim 60 to amended 58.

3.7. Method claims 37 and 39-42, are now dependent, directly or indirectly, on claim 58 and hence, if 58 is deemed allowable, they should be rejoined pursuant to MPEP 821.04. Likewise, new method claims 78 and 79 are dependent on 27 and 67,

respectively.

3.8. Pharmaceutical composition claim 49 is now dependent on 58 and hence, if 58 is deemed allowable, it should be rejoined in accordance with PCT combination/subcombination practice.

3.9. DNA claim 31, vector claim 32 and cell claim 33 are now dependent, directly or indirectly, on claim 58 and hence, if 58 is deemed allowable, should be rejoined pursuant to PCT Administrative Instructions, Annex B, Part 2, Example 17(DNA encoding protein) and Annex B, Part 1, paragraph (c)(general rule concerning dependent claims, including combination claims dependent on a subcombination claim).

3.10. Claims 23 and 25 are drawn to a non-elected species, i.e., one in which the collagen-like domain is from human MBL, whereas the elected species comprises the collagen-like domain of human L-ficolin.

However, these claims are now dependent on claim 58, and if this generic claim is deemed allowable, claims 23 and 25 should be rejoined.

The same is true of new claims 108 and 109.

4. Enablement

The broader claims are rejected for insufficient enablement. We traverse.

It appears that in the specification, applicants disclosed

(1) the complete sequences of seven fusion proteins (SID 118-124) (pp. 100-2 and SID 118-124) and the construction of the expression vectors (Example 1 and Figs. 4-8),

(2) the alignment of SID 118-122 with "MBL-C_HUMAN" and "FCN2_HUMAN@2" (Fig. 9), with the signal sequence, collagen-like domain and MBL CRD domain labeled,

(3) the location of the "coil-coil" of MBL, as incorporated into SID 120 (P101, L21),

(4) the MBL binding activity of the two tested fusions (FCN2MBL r4/SID121, r5/SID 122) (Example 2).

The Examiner questions whether "5-6 fusion proteins" provide adequate support for the "extremely broad genus" of claim 1, which is not limited to a particular lectin-complement pathway activating protein (LCPAP) or to a particular collectin.

The rejection, in addressing the scope of the claims, refers to the possible variation in

(1) the choice of the reference LCPAP,

(2) the choice of the reference collectin,

(3) the choice of the length and location of the fragment within each of (1) and (2), and

(4) the mutation of the fragment within the limit of 70% identity (claim 1) or 95% identity.

4.1. The proposed amendment eliminates the first two sources of variation.

4.2. With regard to the third variation, the required fragment length was previously variously 30 amino acids (claims 1, 66, 69), or 50 (claims 57 and 59), and note also the implicit fragment length limitations of claims 20-29, 67 and 68.

In general, one is more likely to lose activity by using a smaller fragment than a larger one. The logical question, then, is what is the smallest fragment which has activity. In the elected protein, we are combining 77 a.a. from the 288 a.a. L-ficolin with 149 a.a. from the 228 a.a. human MBL.

Referring to Table I of this amendment, and in particular to mutants r1, r4 and r5, we have demonstrated that ficolin fragments smaller than one-sixth full length, and MBL fragments smaller than one-half full length, are useful. Indeed, it is evident that fragments of human L-ficolin as small as 44 a.a. retained activity.

This would appear to put the onus on the examiner to show more specific reason to doubt the operability of the 40 a.a. (L-ficolin) or 50 a.a. (MBL) fragments of claim 58. The Examiner should bear in mind that inoperatively small fragments are explicitly excluded, cp. Ex parte Mark, 12 USPQ2d 1904 (BPAI 1989).

Likewise, the Examiner has no adequate basis to doubt the operability of a fusion of at least amino acids 1-44 of human L-ficolin to at least amino acids 100-200, per claim 67, given the support provided by r1, r4 and r5. The r5 fusion only provided 1-44 of ficolins yet was functional. The r1 mutant provided only 106-228 of MBL (similar albeit not identical to the recited 100-200), yet was functional.

Nor does the Examiner have any adequate basis to doubt the operability of a fusion of at least the collagen-like domain of human L-ficolin to at least the CRD domain of human MBL, per claim 27, again given the support provided by r1, r4 and r5.

4.3. Finally, we come to the issue of mutation. The Examiner cites Rudinger (1976) and Bowie (1990) to the effect that substitutions can destroy activity and it is difficult to predict the effect of mutation.

We respectfully submit that it is nonetheless well accepted that what are called "conservative substitutions" are indeed predictably more likely (albeit not certain) to preserve activity, and that the standard of enablement is an absence of undue experimentation. There are now powerful techniques for rapidly ascertaining the effects of mutation, e.g., alanine-scanning mutagenesis, homologue scanning mutagenesis, and combinatorial libraries, which were in their infancy in 1990 and unknown in 1976.

In addition, the specification identifies many homologous proteins. This guidance cannot be ignored.

Appendix 1 is an incomplete list of U.S. patents with % identity limitations in the 40-90% range.

At the present time, Applicants only seek 95% identity language. Conducting, on March 19, 2008, the search **(aclm/"at least 95 percent identical" or aclm/"at least 95 per cent identical") and aclm/"SEQ ID NO"** on the USPTO database of patent issued since 1976, we obtain 12 hits (Exhibit F). Please note that we can't search on the alternative aclm/"at least 95% identical" because the PTO search software truncates the search

term at the "%".

If the search **aclm/"at least 95% identical" and aclm/"SEQ ID NO"** is conducted on www.freepatentsonline.com , advanced patent search, with only "US Patents" checked, "All Years" specified, and stemming off, we get **679** hits. (Exhibit G[8]).

The cases set forth in Appendix 2 indicate that prior patents can be relevant to patentability.

The Examiner's attention is also respectfully directed to the Written Description Training Materials, Example 14. This said that reduction to practice of a single sequence ("SEQ ID NO:3") was sufficient to establish written description of a claim directed to "a protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B". The PTO noted that procedures for making variants of SEQ ID NO:3 were conventional in the art (i.e., site specific mutagenesis) and that an activity assay was disclosed. It concluded that the claimed genus "does not have substantial variation since all the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO:3".

While written description and enablement are separate disclosure requirements, they are also intertwined, and if a single sequence is representative of the genus defined by a 95% identify limitation coupled with an activity limitation, it seems reasonable to infer that the isolation of 95% identical functional mutants was not likely to require undue experimentation.

The proposed 95% limitation, applied to human L-ficolin (288 a.a.) or human MBL (228 a.a.), allows a maximum of 14 mutations in human L-ficolin or 11 in MBL. Applied to fused fragments, the number of allowed mutations is smaller. For example, using the elected ficolin (1-77)/MBL (80-228) as a guide, the 95% language

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[8] Neither search covers synonymous concepts such as "at least 95% homologous" or "having at least 95% identity", and hence some supporting patents have no doubt been overlooked.

would allow three mutations in the ficolin fragment and seven in the 149 a.a. MBL fragment. If the total fusion protein length were 228 a.a., like human MBL, the maximum total number of allowed mutations would be eleven.

5. Prior Art

5.1. All claims except 30 are rejected as obvious over Thiel "WO 02/06460" [sic, "WO 00/70043", see OA page 10, lines 7-9] and Endo in light of Matsushita.

The Examiner concedes that claim 30, which recites a polypeptide consisting of 1-77 of human ficolin (SID 125) and 80-228 of human MBL, is allowable over the prior art.

5.2. We begin the consideration of obviousness of the rejected claims by addressing the three Graham factors.

5.3. *Level of Ordinary Skill in the Art*. The examiner has not made any findings concerning the level of ordinary skill in the art in connection with the prior art rejection. In connection with the enablement rejection, the June 1, 2007 rejection, page 14, stated that the relative skill is characterized by that of an "M.D. or Ph.D. level individual."

5.4. *Scope and Content of the Prior Art*. The relevant prior art by definition includes at least the references relied on by the rejection.

As pointed out above, the reference to Thiel, WO 02/06460 seem to be in error, with Thiel, WO 00/70043 being intended. See office action page 10, lines 7-9. We hope that the next office action will eliminate the erroneous reference to the '460 application.

"Matsushita" was first relied on in the June 1, 2007 office action as "Matsushita et al. 2002 (cited in the IDS filed March 10,2 005)". There were actually two Matsushita (2002) references, one with page numbers 3502-06 (AM) and the other 490-

97 (AI).

At page 18, last line, of that response, the Examiner cites "page 2281, column 1, lines 1-4" of "Matsushita et al.". That is outside the page range of both 2002 reference, but the 2000 reference (AK) has page numbers 2281-4 and the text in AK is consistent with the office action.

Accordingly, we respectfully request that the next office action clarify which of the three Matsushita references of record is being relied upon, and if more than one is relied upon, which is relied upon for what teaching.

5.5. *Differences Between the Prior Art and the Claimed Invention.*

5.5.1. Thiel was cited as teaching the sequence of human MBL and that MBL can be fused to other proteins. We previously pointed out that Thiel WO 00/06460 teaches fusions of MASP-2, not MBL, to other proteins (last response p. 15), and that Thiel WO 00/70043 likewise does not disclose any MBL fusions.

5.5.2. Endo discloses that human lectin p35 has a particular sequence (313 a.a.) and the Examiner's sequence alignment establishes that it comprises amino acids 1-77 of our L-ficolin (SID 125). There is no teaching in Endo that residues 1-77 are of any particular importance. Endo does disclose the alignment of p35 to three other ficolins.

5.5.3. "Matsushita" allegedly discloses the structural and functional similarities of ficolin with MBL.

With regard to the structural and functional similarities of ficolin and MBL, Matsushita Ref. AI teaches: (1) "MBL consists of collagen-like domain and a carbohydrate-recognition domain" (490); (2) "Ficolins...consisted of collagen-like and fibrinogen-like domains, the latter containing approximately 230 amino acids showing similarity to the COOH terminal halves of fibrinogen beta and gamma chains" (490-1); (3) "Serum ficolins are lectin pathway-activating lectins like MBL" (491); and (4) Ficolins and MBL both consist of collagen-like domain and carbohydrate-binding

domain, although their carbohydrate binding moieties are different (494).

Thus, Matsushita teaches a broad functional similarity (lectin-pathway activation; carbohydrate binding) and some broad structural similarity (collagen-like domain) between ficolins and MBL, but also teaches that there are significant structural differences. We will expand on those structural differences later in this analysis.

Matsushita also sheds some light on the structural similarity among ficolins; L vs. H ficolins, and H vs. M ficolins are 48% identical, L/M are 80% identical (493). Please keep these in mind when we examine, more quantitatively, the structural similarity of ficolins to MBL.

It does not appear to us that Matsushita Refs. AK and AM add anything relevant which is not already in AI.

5.6. The Graham test calls upon the trier of fact to then determine whether the differences between the invention as claimed, as a whole, and the prior art, are such that the claimed invention is obvious or nonobvious. Unfortunately, it doesn't provide much guidance as to how to make that evaluation, other than to warn that the so-called secondary considerations are relevant.

5.6.1. The present claims are directed to fusion proteins, which are complex chemicals. Consequently, we begin this evaluation by following the template established by the Federal Circuit in its recent decision, Takeda Pharmaceutical Co. v. Dudas, 84 USPQ2d 1365 (Fed. Cir., Sept. 18, 2007).

A description of that case may prove helpful. There is a class of drugs, thiazolidinediones (TZDs), which reduce insulin resistance. One such TZD is pioglitazone, the active ingredient in Takeda's ACTOS® drug, and the subject of the challenged claim.

Alphapharm asserted that the claimed pioglitazone was obvious over a known TZD. According to the Federal Circuit, the argument required that the person of ordinary skill in the art

first select that known TZD (called "compound b" in the opinion) as the lead compound, and then make two chemical changes: 1) "homologation," replacement of the methyl group with an ethyl group, and 2) "ring-walking," movement of that ethyl group from the 6-position to the 5-position on the ring.

The district court had found that the skilled worker would not have selected "compound b" as a lead compound for further development. Not only were there prior art patents with claims for TZDs which covered hundreds of millions of compounds, there was a nonpatent reference in which compound b was compared with several other TZDs and was not one of the three TZDs which that reference identified as being the "most favorable." The Federal Circuit agreed with this analysis.

The district court also was not persuaded that even if "compound b" were to be considered a "lead compound," that the skilled worker would have been motivated to make the two required chemical changes because there would not have been a reasonable expectation that either change would have reduced the toxicity or increased the efficacy of compound b.

Finally, the district court considered the low toxicity of pioglitazone to be an unexpected result, given the significant side effects induced by "compound b."

5.6.2. For the claimed fusion protein, which is a fusion of a fragment of human L-ficolin to a fragment of human MBL, either human L-ficolin or human MBL could be considered the lead compound, depending on which one was more structurally similar to the fusion of interest. We consider both possibilities.

Following the guidance of Takeda, we first ask what motivation there would have been for a person of ordinary skill in the art to select human L-ficolin as a lead compound for developing mutant proteins, and in particular, those with the asserted properties of the presently claimed fusion protein. "From the standpoint of patent law, a compound and all of its properties are inseparable". In re Papesch, 137 USPQ 43 (CCPA

1963).

Human L-ficolin and human MBL both have the capability of activating the lectin complement pathway. It is evident from the specification that a very large number of other proteins have this capability. The examiner has failed to make any showing that human L-ficolin or human MBL are superior to other activators of the lectin complement pathway. Hence, the examiner has failed to establish a motivation for choosing either human L-ficolin or human MBL as the lead compound for a program of developing an improved lectin-complement pathway activating protein.

Indeed, the references do not teach **any** designed mutants of human L-ficolin.

With regard to selection of human MBL as a lead compound for the development of mutant proteins, Thiel '043 contains only a very generic teaching of mutants which are "functionally equivalent" to MBL, that is, which activate C4 and/or interact with MBL receptors on cells, see Thiel '043 page 9, lines 14-16. A preference is expressed at page 10, line 28 et seq. for conservative substitutions, but the possibility of other substitutions, and indeed of deletions and insertions, is noted at page 17, lines 3-6. No specific fragments or other mutants are taught.

In general, it appears that the teaching of Thiel with regard to mutants is not that human MBL can be used as a lead compound for the purpose of producing an **improved** protein, but rather to ensure that the claimed subject matter encompasses "equivalents" of MBL. However, the claimed fusion protein is more than a mere "equivalent" of MBL.

5.6.3. We turn next to the issue of the modification. Assuming first that the lead compound is human L-ficolin, the following modifications are required to arrive at the compound of claim 58:

(1) omission of one or more amino acids of human L-ficolin

(since the claim recites a fragment),[9] and

(2) addition of at least fifty amino acids of MBL.

Claim 27 would instead require addition of the at least the CRD domain of MBL, and claim 67, of at least amino acids 100-200 of MBL.

Assuming instead that the lead compound is human MBL, the following modifications are required to arrive at the compound of claim 58:

(1) omission of one or more amino acids of human MBL (since the claim recites a fragment), and

(2) addition of at least forty amino acids of human L-ficolin.

Claim 27 would instead require addition of at least the collagen-like domain of human L-ficolin, and claim 67, of at least amino acids 1-44 of human L-ficolin.

None of the cited prior art teaches omission of any part of human L-ficolin. Nor does any of the cited prior art suggest modification of human L-ficolin to include any portion of human MBL.

While Thiel admits of the possibility of deleting or replacing residues of human MBL, or of adding residues to MBL, it makes no specific teachings as to the nature of these modifications and in particular does not teach addition to MBL of any portion of human L-ficolin.

The structural and functional similarity of human L-ficolin and human MBL is of too attenuated a nature to have motivated the person of ordinary skill in the art to fuse a fragment of human

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[9] Some dependent claims are more specific as to which human L-ficolin elements, or how much of its sequence, must be omitted.

L-ficolin to a fragment of human MBL, as claimed.

When mature human L-ficolin and mature human MBL are globally aligned with GAP (no penalty for end-gaps), using the software at genome.cs.mtu.edu/align.html, the level of percentage identity ("match percentage") is only 9% (Exhibit E). The matches are entirely in the amino terminal region (AA 1-72 of L-ficolin and 1-70 of MBL), as would be expected given that both L-ficolin and MBL have N-terminal cys-rich regions and collagen-like domains.

However, these remotely homologous regions are not sufficient for complement-activating activity.

When the same sequences are locally aligned with SIM (default settings), using the software at the same website, the best local alignment (Begins at (28, 21) and Ends at (72, 70)) has a similarity Score of 124, a percentage identity ("Match Percentage") of 52%, with a total internal gap length of 5. (Exhibit E)

Just to put that similarity score of 124 in perspective, if mature human L-ficolin were aligned with itself, the SIM similarity score would be 1607. And even if just the fragment acids human L-ficolin *(28-72) was aligned with itself, the similarity score would be 264.

The second best local alignment (Begins at (3, 8) and Ends at (68, 69)) has a similarity score of 118, a percentage identity of 44%, a total internal gap length of 8.

All of the top five local alignments are directed to essentially the same (amino-terminal) region.

Given the limited homology even in that amino terminal region, and the great divergence between the sequences outside that region, we respectfully submit that it would not have been obvious to modify either human L-ficolin or human MBL by fusing to it a substantial portion (at least 40 amino acids) of the other protein.

We note that in the context of the enablement rejection, the

examiner did not concede that even a 95% identical substitution mutant of a protein could be expected to have the claimed functionality. If that protein were the size of human L-ficolin, it would be 288 amino acids, and the maximum number of substitutions would be 14. (Human MBL is smaller.)

If the examiner could doubt that the skilled worker, even given the guidance of applicant's specification, could make a functional substitution mutant, changing at most 14 amino acids, of the contemplated human L-ficolin/human MBL fusions, how could the skilled worker, **lacking such guidance** and based only on the prior art relied on, have reasonably expected to successfully modify human L-ficolin or human MBL into a functional fusion protein by **adding forty or more amino acids** of the other protein?

5.7. Even if prima facie obviousness were shown for the subject matter as presently claimed, it is rebutted by applicants' evidence of unexpectedly superior results for the claimed fusion proteins.

As already argued in our previous response, figure 10 and the specification on page 107, lines 5-9 show that , in contrast to MBL, which occurs in a wide range of oligomeric forms, the most prominent form of the tested L-ficolin/MBL fusions has a size of about 250 kDa. This result is confirmed by Michelow, et al., fig. 1B (Exhibit D).

Thus, these fusion proteins retain the ability of MBL to bind to and activate MASP-2, but they have the advantage of a simpler oligomeric structure.

5.8. We next direct the Examiner's attention to certain dependent claims, 99-101:

> 99. (New) The fusion protein of claim 27, which does not comprise the fibrinogen-like domain of human L-ficolin.

100. (New) The fusion protein of claim 27, which does not comprise the cysteine-rich region of human MBL.

101. (New) The fusion protein of claim 100, which does not comprise the collagen-like domain of human MBL.

The art relied on does not motivate one modifying L-ficolin to omit the fibrinogen-like domain. The art relied on does not motivate one modifying human MBL to omit the cysteine-rich region or the collagen-like domain of that protein.

Prior to applicant's construction and testing of the r4 and r5 mutants, there would not have been a reasonable expectation that the essential replacement of the fibrinogen-like domain of human L-ficolin with the CRD domain of human MBL would result in a functional fusion protein, i.e., one capable of activating the complement pathway. There is essentially no homology between these two domains, and the fibrinogen-like domain is highly conserved among the L-ficolins.

Likewise, there would not have been a reasonable expectation that the essential replacement of the cysteine-rich region of human MBL and/or the collagen-like domain of human MBL with the corresponding regions of human L-ficolin would result in a functional fusion protein. While there is a higher homology between the N-terminal regions than between the C-terminal regions, it is still on the order of only 50% identity.

6. Miscellaneous

In the course of preparing table 1, it came to our attention that the MISC_FEATURE information for SEQ ID NOS: 118-124 was not accurate. The correct information is in table 1, and was ascertained by comparison of SEQ ID NOS: 118-124 with SEQ ID NO: 125 (mature human L-ficolin) and SEQ ID NO: 126 (mature human MBL). Since the submission of MISC_FEATURE information is optional, we weren't sure whether the examiner would prefer that

we leave the rather voluminous sequence listing as is, correct the MISC_FEATURES on the basis of the analysis in Table 1 (the numbering will be somewhat different since SEQ ID NOS: 118-124 include signal sequences) or to merely delete those MISC_FEATURES (and, if so, should we add a MISC_FEATURE identifying the signal sequence). The Examiner's advice is earnestly solicited.

Respectfully submitted,

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Enclosure
-Exhibit A: Swiss-Prot entry MBL2_HUMAN (P11226)
-Exhibit B: Swiss-Prot entry FCN2_HUMAN (Q15485)
-Exhibit C: Fig.. 2, "Domain and oligomeric structure of mannose-binding lectin and ficolins," from Fujita, "Evolution of the lectin-complement pathway and its role in innate immunity," Nature Reviews Immunology 2: 346-53 (May 2002).
-Exhibit D: Michelow, et al., "Recombinant human mannose-binding lectin (MBL) and novel chimeric molecules derived from MBL and L-ficolin to treate Ebola virus infections," poster submitted for Filomeeting 2008, Filovirus Global Symposium, March 26, 27 & 28, 2008 in Libreville, Gabon.
-Exhibit E: Sequence comparison using GAP and SIM
-Exhibit F: USTPO patent database search
-Exhibit G: freepatentsonline database search
-Appendix 1, 2 and 3

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Appendix 1: US Patents with Claims Characterizing Mutants by % Identity to Reference Sequence	
Patent/claim	**%**
USP 5,304,640 claim 2	40%
Bell, USP 4,761,371 claim 8	40%
Holtzman 6,410,232	55%
Wang, 6,639,051 claim 17	60%
Yurchenko 6,632,790 claim 2	70%
USP 5,670,335	70%
USP 5,538,892	70%
Deeley, USP 5,489,519	70%
Tarczynski 6,372,961	70%
Stafford, USP 5,268,275 claim 13	75%
Hoffman, USP 5,545,727 claim 9	75%
Sheppard, 6,265,544	75%
Sheppard, 6,498,235	80%
Mahajan 6,388,169	80%
Williams, 6,642,022	80%
Friedman 6,429,290	83%
Hayden 6,617,122 claim 33	85%
Bertin, 6,482,933	85%
Sim 6,482,403	85%
Crabtree 6,388,052	90%
Raju 6,500,654 claim 10	90%
Acton 6,436,685	90%
Cerretti RE37,582	90%

Appendix 2

Ex parte Brian, 118 USPQ 242, 245, (POBA 1958) (past practice of office in accepting definiteness of "fingerprint" claims);

In re Chakrabary, 596 F.2d 952, 985-86 (CCPA 1979) (product claims reciting microorganisms previously treated as directed to statutory subject matter);

Andrew Corp. v. Gabriel Electronics, Inc., 6 USPQ 2010, 2012 (Fed. Cir. 1988) (term "substantially" is "ubiquitous" in patent claims and therefore considered definite);

In re Cortright, 49 USPQ2d 1464 (Fed. Cir. 1999) (Construction of "restore hair growth" for purpose of determining both §112 enablement and §101 utility; prior art references may be indicative of how a claim term will be interpreted by those of ordinary skill in the art);

Vitronics Corp. v. Conceptronic Inc., 39 USPQ2d 1573, 1578-9 (Fed. Cir. 1996) (prior art used to demonstrate how a disputed term is used by those skilled in the art, and indeed is more objective and reliable than post-litigation expert opinion testimony);

Pioneer Hi-Bred International v. J.E.M. Ag Supply Inc., 49 USPQ2d 1813, 1819 (N.D. Iowa 1998) (issuance of Boehm USP 2,048,056 in 1936 is evidence that "in those instances where inventors showed they could define a reproducible plant meeting the limits of §112, plant patents were issued under §101".)

Appendix 3

Table III Overview of Fusion Protein Claims						
Cl	Dp	Ficolin Content	Min %ID	MBL Content	Min % ID	Comment
58	-	>=40 a.a.	95%	>=50 a.a.	95%	
3	58					functional lim.
4	58					functional lim.
15	58	comp. 1-77	100%			P19, L12
21	58			comp. CRD	100%	P19, L32
23	58			comp. collagen-like domain	100%	P82, L2-7; PP83-84
24	58			comp. neck + CRD	100%	"
25	58			comp. collagen-like domain		"
26	58			comp. 80-228	100%	P82, L21
29	58	comp. SEQ ID NO:127			95%	
30	58	1-77	100%	80-228	100%	elected species
56	58	at least five XGXXG	-			P19, L20-21
61	58					conserv sub
76	58	≥40 a.a.	100%	≥50 a.a.	100%	
77	58	≥50 a.a.	95%	≥50 a.a.	95%	
78	77	≥50 a.a.	100%	≥50 a.a.	100%	
86	58	& comp. 1-27	100%			location of 2d Cys per P11, L18; cp. SID 125

87	58	see discussion	95%	at least CRD	95%	see discussion
88	87	& Cys-rich	95%			
89	87	&neck?		&neck?		see discussion
102	58					& signal seq P100, L25
103	102					Id
104	58	as for 58	99%	as for 58	99%	P88, L16
105	58					at most 1 sub 97% of 40 a.a. allows just 1 sub; 96% of 50 a.a. allows just 1 sub; cp. P88, L10-11.
106	58					at P85, L10 most 1 conserv sub
107	58	at least 44 AAs		at least 185 AAs		SID 122
108	58	at least 57 AAs		at least 173 AAs		SID 121
109	58	at least 103 AAs		at least 123 AAs		SID 118
110	58	at least 77 AAs		at least 149 AAs		SID 127
111	58	at least 44 AAs		at least 123 AAs		SID 118, 122
112	72		100%		100%	cys-rich and neck, total at least 226AAs; cp. SID 118
27	-	comp. collagen-like domain	95%	comp. CRD domain	95%	
22	27	"		&comp. neck	100%	
70	27	"	100%	comp. CRD domain	100%	

71	27	&comp. Cys-rich	95%	"	95%	
72	70	"		"	100%	equivalent to old 27
73	72	"		& comp. neck	100%	22+72
74	27	comp collagen-like domain	95%	comp CRD domain	95%	conserv sub.; 27+61
75	71	& comp. Cys-rich	95%	"	95%	conserv sub.; 71+61
99	27	no fibrinogen-like domain				cp. P4, L35 with P11, L5-22 and PP83-84
100				no Cys-rich region		PP83-84
101				& no collagen-like domain		PP83-84
67	-	comp. 1-44	95% comp.	100-200	95%	SID 122
63	67	comp. 1-44	95% comp.	100-200	95%	conserv sub
68	67	comp. 1-44	100%	100-200	100%	
79	67	comp. 1-54	95%	100-200	95%	P19, L5
80	67	comp. 1-54	100%	100-200	95%	
81	67	comp. 1-57	95%	"	"	SID 121
82	67	comp. 1-57	100%	"	"	
83	67	comp. 1-103	95%	"	"	SID 118
84	67	comp. 1-103	100%	"	"	
85	67	comp. 1-77	95%	"	"	P19, L12